Journal of Asian Scientific Research

journal homepage: http://aessweb.com/journal-detail.php?id=5003

A RARE FOUR SUPERNUMERARY NOSTRIL: A FEMALE CASE REPORT AT THE HOSPITAL PARA EL NIÑO POBLANO, MÉXICO

Aparicio-Rodríguez J. M

Genetics, Universidad Autónoma Metropolitana, México. Estomatology

Urzaiz E

Otorynolaringology

Rodríguez-Peralta S

Neurosurgery

San Martin Brieke W

Maxilar surgery

Zepeda-Olivera S

Anesthesiology

Chatelain-Mercado S

Hospital para el Niño Poblano, México. Biotechnology

ABSTRACT

Supernumerary nostril is considering a rare congenital craniofacial disorder, which includes two additional nostrils without upper respiratory communication, as the case in this study, where three nostrils were located at the medial lineal, whether the fourth nostril was located near the right eye. All cavities were around 3 mm diameter and one accessory upper lateral cavity around 5 mm. Two cavities were lined with mucous membrane and filled with mucoid discharge. Nasal endoscopy of cavities showed that they were small as compared to a normal nasal cavity and only two communicate with upper air respiratory system. Normal cytogenetic analysis was observed 46XX. The supernumerary nostrils may occur due to an alteration to the homebox genes, taking in consideration that morphogenesis depends on these genes integrity during fetal growth.

Keywords: Supernumerary nostril, Genetics, Congenital anomaly, Nasal process alteration

INTRODUCTION

Supernumerary nostrils are extremely rare congenital disorder. Only 21 published cases since 1906 has been published, Franco *et al.* (2008). It has been reported as unilateral or bilateral in some occasions. However Lindsey in 1906 studied the first documented patient with bilateral supernumerary nostril, as Tawse (1920) found a patient with a unilateral supernumerary nostril that

communicated with the nasal cavity. In 1987 Reddy and Rao had a case with a third nostril situated below the left nostril. It has also been associated ophthalmological alterations as micro cornea and congenital cataract (Sinha *et al.*, 2005) with supernumerary nostril in a patient. In the present case report, we are describing a case of a patient with a craniofacial deformity that clinically corresponds either to supernumerary nostril or a variety of arrinea called "proboscis lateralis", a malformation which has its origin in the nasal placoda. However, clinically different to the case in this study **Figures 1.A, B**. This alteration may be accompanied by other complex malformations of the nasal region as imaging studies showed it in this case: absence of floor of skull between the sphenoid and frontal region with apparent occupation of which corresponded to nasal cavity with brain tissue and choanal atresia **Figures 1.A, B**. **Figures 2.A, B.** All these cases because of their complexity, required a multidisciplinary management with a variety of studies as Computed tomography of the skull **Figures 3, Figures 4** and simple XR studies **Figure 5** before Cranio-facial surgery, where neurosurgeons, otorynolaringologists, plastic and Maxillofacial surgeons were involved as well as skilled anesthesiologist during surgical procedures.

By performing genetics studies, a karyotype **Figure 6** was done to analyzed all chromosomes structures looking for deletions, translocations or a different kind of aberrations, especially at chromosomes 2, 7 and 17, where the Homebox genes **Figure 7** *Dlx* are located (craniofacial morphogenesis genes). Panganiban and Rubenstein (2002).

Any of various DNA sequences containing about 180 nucleotides that encode for corresponding sequences of usually 60 amino acids **Figure 7**, called *homeodomains*, found in proteins that bind DNA and regulate gene transcription. Genes containing homeoboxes are found in all eukaryotic genomes and are associated with cell differentiation and bodily segmentation during embryologic development and have been associated to human morphogenesis. As an example of craniofacial morphogenesis development, Dlx genes cluster have been observed. *Dlx* belongs to a family of homeodomain transcription factors, investigated in *Drosophila distal-less (Dll)* gene Panganiban and Rubenstein (2002).

Which are associated to different organisms developmental features. Vieux-Rochas *et al.* (2007), Vieux-Rochas *et al.* (2010), these factors has been observed to be preserved across species. Stock *et al.* (1996) Including Dlx1 to Dlx7 genes. They form big gene clusters all together. There are Dlx1-Dlx2, Dlx5-Dlx6 and Dlx3-Dlx7 (or Dlx4 in mouse) clusters found in vertebrates. All mentioned genes are associated to Hox gene cluster. In higher fishes, like Zebrafish, there are a couple of additional *Dlx* genes, *Dlx5* and *Dlx8*. In zebrafish the orthologous genes to vertebrate *Dlx5-Dlx6* are *Dlx4* and *Dlx*6. *Dlx4*, *Dlx7*, *Dlx8* and *Dlx9* are the same genes as in vertebrates. Homebox genes. Panganiban and Rubenstein (2002) hamper the proper functioning of the caudal cell mass of the fetal mesoderm as the craniofacial bones separates from each other to give rise the different facial structures. Different body tissues might be miss formed depending on the homebox genes information, as it has been investigated in some cases of ambiguous genitalia were penis duplication was observed in some patients. Aparicio-Rodríguez *et al.* (2010), Camacho-Gutierez *et*

al. (2004). It is commonly mistaken that all sharks have this condition, but in reality they have a pair of "claspers", which serve a reproductive function.

MATERIAL AND METHODS

A 22-year-old mother, pregnancy with prenatal care, premature birth. Product obtained through abdominal surgery, weight at birth of 2, 490grs diagnosed as craniofacial deformity. Several studies were performed in this pediatric patient with supernumerary nostril. The karyotyping was carried out using blood after Giemsa Banding (GTG) banding of chromosomes with enzymes and stains that was performed according to national and international standard procedures on peripheral blood lymphocytes from the patient. imaging studies were also performed.

DISCUSION AND CONCLUSIONS

Among homebox genes **Figure 7**, *Dlx* genes are involved in craniofacial morphogenesis Beverdam *et al.* (2002), Depew *et al.* (2002), (Vieux-Rochas *et al.*, 2010) and the tangential migration of interneurons from the subpallium to the pallium were vertebrate brain started developing Anderson *et al.* (1997). *Dlx* promotes the normal craniofacial development and the migration of interneurons by repressing a set of proteins that are normally expressed in terminally differentiated neurons and begins promoting the outgrowth of dendrites and axons Cobos *et al.* (2005). Mice lacking DLX1 have been observed with delayed-onset epilepsy Cobos *et al.* (2007). As well as DLX2 that has been associated with the development of the zona limitans intrathalamica and the prethalamus. *Dlx5* and *Dlx6* genes are necessary for normal upper and lower jaw and facial formation in vertebrates, Beverdam *et al.* (2002), Depew *et al.* (2002) and DLX7 is expressed in bone marrow Takashi *et al.* (1997).

Homeobox protein **DLX-1** is a protein that in humans is encoded by the *DLX1* gene Simeone *et al.* (1994). Homeobox protein This **DLX1** gene encodes a member of a homeobox transcription factor gene family similar to the *Drosophila* melanogaster distal-less gene. The encoded protein is localized inside the nucleus where it may works as transcriptional regulator of signals from multiple transformin growth factor beta (TGF-β). The specific protein may play a role in the control of craniofacial morphogenesis and the differentiation and survival of inhibitory neurons in the forebrain. This gene is located on the long arm of chromosome 2 **Figure 8**. *wikipedia.org/wiki/DLX1/DLX2/DLX3/DLX4/DLX5/DLX6.* **DLX-2** is a protein that in humans is encoded by the *DLX2* gene. Ozcelik *et al.* (1992). DLX2 work togetjer with another genes as DLX5, MSX1 and Msh homeobox 2 Zhang *et al.* (1997). These homeo box-containing **DLX2**genes have been also studied on Drosophila Melanogaster. As mentioned before, members of the Dlx gene family contain a homeobox that expressed in the head and limbs of the developing fruit fly. The Distal-less (Dlx) family of genes comprises at least 6 different members, DLX1-DLX6. The DLX proteins are postulated to play a role in forebrain and craniofacial development

and are also located as DLX1, on the long arm of chromosome 2 **Figure 8**. *wikipedia.org/wiki/DLX1/DLX2/DLX3/DLX4/DLX5/DLX6.*

Dlx-3 is an important regulator of hair follicle differentiation. Dlx3 regulate role for bone morphogenic protein **(BMP)** during hair development Hwang *et al.* (2008), Park and Morasso (2002). Homeobox protein**.** Many vertebrate homeo box-containing **DLX3** genes expressed in the head and limbs of the Drosophila, and is located on the long arm of chromosome 17 **Figure 10**. *wikipedia.org/wiki/DLX1/DLX2/DLX3/DLX4/DLX5/DLX6.* Mutations in this gene are associated with both trichodentoosseous syndrome (TDO) and amelogenesis imperfecta (AI). Scherer *et al.* (1995). **DLX-4** is a protein that in humans is encoded by the *DLX4* gene. Many vertebrate homeobox-containing **DLX4** have also expression in the head and limbs of the developing fruit fly. Studies of the two splice variants revealed that one encoded isoform, a repressor of the beta-globin gene, located on chromosome 17 **Figure 10**. *wikipedia.org/wiki/DLX1/DLX2/DLX3/DLX4/DLX5/DLX6.*

DLX-5 has been shown to interact with DLX2, MSX1 and MSX2. Simeone *et al.* (1994), Zhang *et al.* (1997) Mutations in the *DLX5* gene have been shown to be involved in the hand and foot malformation syndrome (ectrodactyly). Shamseldin *et al.* (2011), and play a role in bone development and fracture healing. This genes is also located on the chromosome 7 **Figure 9**. *wikipedia.org/wiki/DLX1/DLX2/DLX3/DLX4/DLX5/DLX6.* And finally **DLX-6** is a protein that in humans is encoded by the *DLX6* gene. Simeone *et al.* (1994). This **DLX6** gene encodes for forebrain and craniofacial development, also located on chromosome 7 **Figure 9**. *wikipedia.org/wiki/DLX1/DLX2/DLX3/DLX4/DLX5/DLX6.*

In relation to craniofacial development, the mesenchyme covering the caudal surface of the forebrain proliferates with surface ectoderm to form frontonasal process and the two ectodermal thickenings (nasal placodes) arise on each side of the depedent part of the frontonasal process (Johnson, 1989). Subsequently the depression develops in the surrounding mesenchyme on each side of the two nasal placodes to form the olfactory pits. These olfactory pits separates the frontonasal process into a medial and two lateral processes to form the primitive nasal cavity, while lateral nasal process forms the alae of the nose (Brown and Brown, 1998). The supernumerary nostril is result of the erroneous developmental process among the formation of the nose and nasal cavity, which may be in the form of total duplication of the nasal placode or the fissuring of the lateral nasal process as the patient in this study. The supernumerary nostril is exceedingly rare congenital anomaly of unclear etiology. However it has been demonstrated that alterations in DLX genes located at chromosomes 2, 7 and 17, could be an answer for its etiology. Many authors have been reported a iwde variety of nose duplicactions, as Erich (1962) reported a case of double nose and supported Lindsey (1906) of the dichotomy by atavism or parallel evolution. Onizuka and Tai (1972), reported the case of a single accessory nostril that had developed above the nasal ala. The random fissuring of the lateral nasal process during fetal development will yield unilateral and asymmetric deformity (Nakamura and Onizuka, 1987; Chen and Yeong, 1992; Williams *et al.*,

1998). Hallak *et al.* (2001) reported a case of supernumerary nostril with blind nasal cavity in a normally developed nose. Zbar *et al.* (2003) reported a case of - supernumerary nostril with extra lower lateral cartilage and also supported the theory embryological fissuring of the lateral nasal process. Sinha *et al.* (2005) reported a case of supernumerary nostril with microcornea and congenital cataract and speculated that anomaly in development of the nasal placodes is the cause. If compared to the female patient **FIGURES 1 A, B** in this study, with hypertelorism, palpebral fissures and small eyelids in both eyes. Three nostrils lined up about what would correspond to the nasal dorsum. A fourth nostril in the right supraciliar area. Requested imaging studies **FIGURES 3, 4** where it can be seen abnormalities in the frontal bone formed by 3 segments and in the sagital view, there is not bone floor at the skull. Communication to the nasopharynx is not observed. It is not possible to identify nasal structures by the cavity malformation. Neurosurgery decides to resects the middle segment of the frontal bone. Tracheostomy was performed in order to prepare for surgery. Craneoplasty was then performed without any complications. Before the procedure nasal cavity was explored with flexible endoscope finding no communication to the nasopharynx. Fundoplication and Gastrostomy was then performed. Antibiotic scheme with Vancomycin and cefotaxime was used as prophylactic treatment. This kind of patients requires as mentioned before, a multidisciplinary team as neonatologists, geneticists, endocrinologists, surgeons (otorynolaringologist, plastic, reconstructive, maxillofacial, neurosurgery, etc), counselors, physiologists and ethicists. The goal is to provide appropriate medical support and counseling regarding care and therapy. The earlier the diagnosis and treatment is done, the best of the physical, sociological and psychological life for the patient as in this study, taking in consideration that the diagnosis could be missed during her ultrasound periodical studies. This might be an important issue as mentioned before the earlier treatment is performed the better quality of life will be offer to the patient.

ACKNOWLEDGMENTS

The authors would like to thank the Director of the Hospital Para El Nino Poblano, Dr. Jose Luis Penaloza y Senties and the Director of the Faculty of Estomatology from the Autonomous University of Puebla, Mtro. Jorge A. Albicker Rivero, for their incondicional support.

REFERENCES

Anderson, S., D. Eisenstat, i.L. Sh and J. Rubenstein, 1997. Interneuron migration from basal forebrain to neocortex: Dependence on dlx genes. Science, 278(5337): 474–476.

Aparicio-Rodríguez, J.M., F. Cuellar-López, Hurtado-Hernández ML, arrientos-Pérez M, Reynoso de Mendoza S, Vargas-González R, Camacho-Gutiérrez S. F, Marroquin-Garcia I, C.-M. S. and S.-P. F., 2010. Disorders of sexual development in genetic pediatrics. Three different ambiguous genitalia cases report from

hospital para el nino poblano, mexico. International Journal of Genetics and Molecular Biology 2(8): 182-189.

Beverdam, A., G.R. Merlo, Paleari L., Mantero S., Genova F., Barbieri O., Janvier P. and L. G., 2002. Jaw transformation with gain of symmetry after dlx5/dlx6 inactivation: Mirror of the past? genesis, 34: 221–227.

Brown, K. and O.E. Brown, 1998. Congenital malformation of the nose. 3rd Edn., Mosby,St. : Louis.

Camacho-Gutierez, S., C. Olvera-Caballero, Barrientos-Perez M and J. Aparicio-Rodriguez, 2004. Genitourinary reconstruction in a case of penis duplication associated to bladder duplication, perineal hypospadias and bowel sequestration. Rev Mexicana de Urologia, 64: 135-138.

Chen, M.T. and E.K. Yeong, 1992. Supernumerary nostrils. Br. J. Plast. Surg, 45: 557-558.

Cobos, I., U. Borello and J. Rubenstein, 2007. Dlx transcription factors promote migration through repression of axon and dendrite growth. Neuron, 54(6): 873–888.

Cobos, I., M. Calcagnotto, A. Vilaythong, M. Thwin, J. Noebels, Baraban SC and R. JL., 2005. Mice lacking dlx1 show subtype-specific loss of interneurons, reduced inhibition and epilepsy. Nat Neurosci, 8(8): 1059–1068.

Depew, M., T. Lufkin and J. Rubenstein, 2002. Specification of jaw subdivisions by dlx genes. Science, 298(5592): 381–385.

Erich, J.B., 1962. Nasal duplication: Report of case of patient with two noses. Plast. Reconst. Surg, 29: 159-166.

Franco, D., J. Medeiros, P. Faveret and T. Franco, 2008. Supernumerary nostril: Case report and review of the literature. J Plast Reconstr Aesthet Surg, 61(4): 442-446.

Hallak, A., H. Jamjoom and T. Hosseinzadeh, 2001. Supernumerary nostril: A case report and review. Aesthetic. Plast. Surg, 25: 241-243.

Hwang, J., T. Mehrani, Millar SE and M. MI, 2008. "Dlx3 is a crucial regulator of hair follicle differentiation and cycling. Development 135(18): 3149–3159.

Johnson, K.E., 1989. Development of the face, oral cavity, and pharyngeal pouches. New York: John Wiley and Sons.

Lindsey, B., 1906. A nose with supernumerary nostrils. Trans. Pathol. Soc. Lond.

Nakamura, K. and T. Onizuka, 1987. A case of supernumerary nostril. Plast. Reconst. Surg.

Onizuka, K. and Y. Tai, 1972. Supernumerary nostril Acase report. Plast. Reconst. Surg., 50:403-5. .

Ozcelik, T., Porteus MH, Rubenstein JL and F. U, 1992. Dlx2 (tes1), a homeobox gene of the distal-less family, assigned to conserved regions on human and mouse chromosomes 2". Genomics, 13(4): 1157-1161.

Panganiban, G. and J. Rubenstein, 2002. Developmental functions of the distal-less/dlx homeobox genes. Development 129(20): 4371-4386.

Park, G. and M. Morasso, 2002. Bone morphogenetic protein-2 (bmp-2) transactivates dlx3 through smad1 and smad4: Alternative mode for dlx3 induction in mouse keratinocytes. Nucleic Acids Res, 30(2): 515-522.

Scherer, S., Heng HH, Robinson GW, Mahon KA, Evans JP and T. LC, 1995. Assignment of the human homolog of mouse dlx3 to chromosome 17q21.3-q22 by analysis of somatic cell hybrids and fluorescence in situ hybridization. Mamm Genome 6(4): 310-311.

Shamseldin, H., Faden MA, Alashram W and A. FS, 2011. Identification of a novel dlx5 mutation in a family with autosomal recessive split hand and foot malformation. J Med Genet 49(1): 16-20.

Simeone, A., Acampora D, Pannese M, D'Esposito M, Stornaiuolo A, Gulisano M, Mallamaci A, Kastury K, Druck T and e.a. Huebner K, 1994. Cloning and characterization of two members of the vertebrate dlx gene family. Proc Natl Acad Sci U S A 91(6): 2250-2254.

Sinha, R., S. Das, B. Sikder, S. Ray and U.K. Bit, 2005. Supernumerary nostril with congenital cataract. Ear Nose Throat J, 84: 116-119.

Stock, D., Ellies DL, Zhao Z, Ekker M, Ruddle FH and W. KM., 1996. The evolution of the vertebrate dlx gene family. Proc Natl Acad Sci U S A. 93 (20): 10858–10863, 93(20): 10858-10863.

Takashi, S., Shuji Nakamura, Jacques Bollekens, Frank H. Ruddle and K. Takeshita, 1997. Inhibition of dlx-7 homeobox gene causes decreased expression of gata-1 and c-myc genes and apoptosis. Proc Natl Acad Sci U S A, 94(7): 3245-3249.

Tawse, H.B., 1920. Supernumerary nostril and cavity. Proc. R. Soc. London.

Vieux-Rochas, M., Bouhali K., Baudry S., Fontaine A., Coen L. and L. G., 2010. Irreversible effects of retinoic acid pulse on xenopus jaw morphogenesis: New insight into cranial neural crest specification. Birth Defects Research (Part B), 89: 493-450.

Vieux-Rochas, M., S.T. Coen L., Kurihara Y., Gitton Y., Barbier O., Le Blay K., Merlo G.R., Ekker M., Kurihara H., Janvier P. and L. G., 2007. Molecular dynamics of retinoic acid-induced craniofacial malformations: Implications for the origin of gnathostome jaws. PlOSOne. 2 (6): e510., 2(6): e510.

Vieux-Rochas, M., Mantero S., Heude E., Barbieri O., Astigiano S., Couly G., Kurihara H., Levi G. and M. G.R., 2010. Spatio-temporal dynamics of gene expression of the edn1-dlx5/6 pathway during development of the lower jaw. Genesis, 48: 362-373. Available from wikipedia.org/wiki, wikipedia.org/wiki/DLX1/DLX2/DLX3/DLX4/DLX5/DLX6.

Williams, A., M. Pizzuto, L. Brodsky and R. Perry, 1998. Supernumerary nostril: A rare congenital deformity. Int. J. Pedia. Otorhinolaryngol, 44: 161-161.

Zbar, R.I., S.M. Rai and P. Ghimire, 2003. Repair of congenital nasal anomalies involving redundancy of structures. Cleft Palate Craniofac. J, 40(2): 214-211.

Zhang, H., Hu G, Wang H, Sciavolino P, Iler N, Shen MM and A.-S. C, 1997. Heterodimerization of msx and dlx homeoproteins results in functional antagonism. Mol. Cell. Biol, 17(5): 2920-2932.

FIGURE LEYENDS

Figures 1.A, B. **A**.The patient, shows severe telecanto due to cleavage and brain structure, palpebral fissure left with antimongoloid phenotype due to malformation on the left side within normal limits. Both eyes with normal vision. **B.** one malformated nostril and the nose absence with a plane face.

Figures 2 A, B, C. Craniofacial tessier 0-1-2-3, characterized by lack of fusion of the frontal and nasal bones, phenotipically presents 4 holes of which one of the nares with ectopic presentation locates in the right fronto orbital rim l, right with communication ectopic a nasal cavity, the 3 left nares were aligned in the mid-line, 2 of them with no nasal communication.

Figure 3. Computed tomography of the skull showing the craniofacial defect with bone absence at the craneal base and atresic coanas.

Figure 4. Computed tomography of the skull is showing the craniofacial defect with the presence of 3 structures bone separated. The pictures from 3, 4, 5, 6 to 7 (from left to right), show the few air quantity inside the malformed nose cavity.

Figure 5. No further malformations were observed both in thorax neither abdomen structures.

Figure 6. Chromosomal studies showed a normal DNA complement, where neither deletion nor translocations were observed. Especially chromosomes 2, 7 and 17 were homebox XL1 to KL6 genes (craniofacial morphogenesis genes) are located.

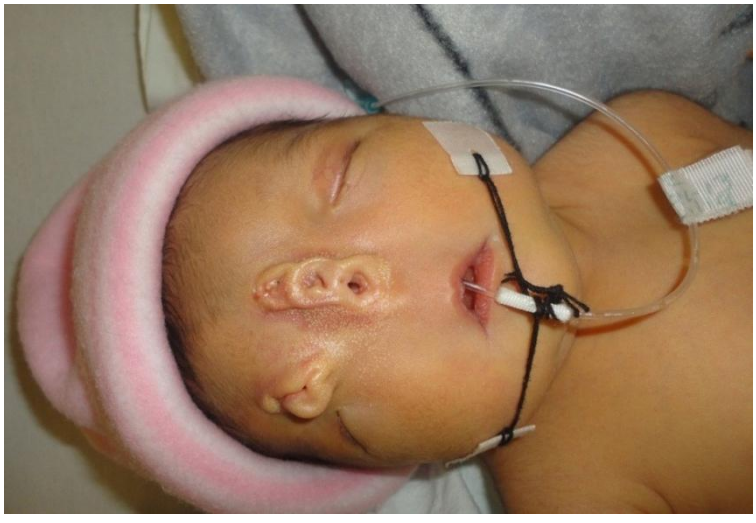
Figure 7. Homeodomain. Amino acids in length (180 base pairs). It is encoded by the homeobox. Reference; Meyers of the encyclopedia of molecular medicine

Figure 8. Chromosome 2 is the second largest human chromosome, spanning more than 243 million base pairs and representing almost 8% of the total DNA in cells. The estimated number of genes varies. Chromosome 2 likely contains 1,491 genes, including those of the HOXD homeobox gene cluster. wikipedia.org/wiki/DLX1-2.

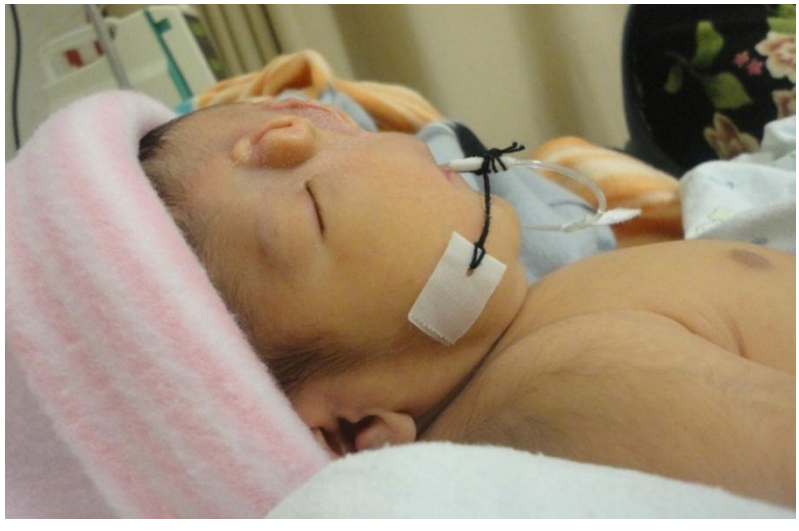
Figure 9. Chromosome 7 spans more than 158 million base pairs and represents between 5 and 5.5 percent of the total DNA in cells. the estimated number of genes varies. Chromosome 7 is likely to contain between 1,000 and 1,400 genes. It also contains the Homeobox A gene cluster. wikipedia.org/wiki/DLX3-4.

Figure 10. Chromosome 17 spans more than 81 million base pairs and represents between 2.5 and 3% of the total DNA in cells.The estimated number of genes varies. Chromosome 17 likely contains between 1,200 and 1,500 genes. It also contains the Homeobox B gene cluster. wikipedia.org/wiki/DLX 5-6.

Figures-1.

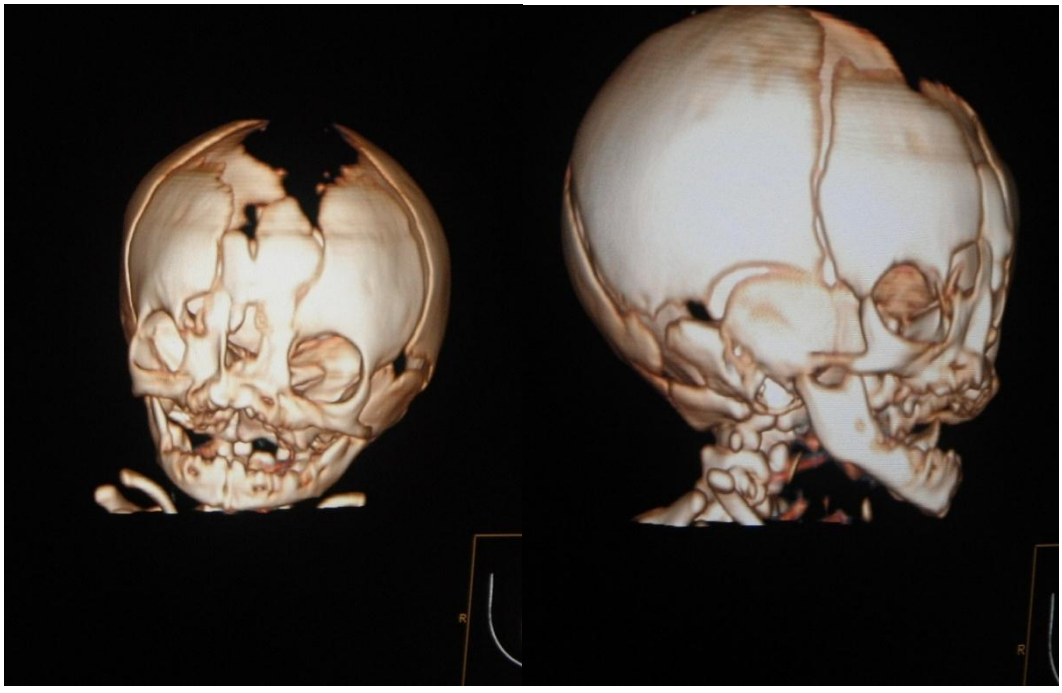


A

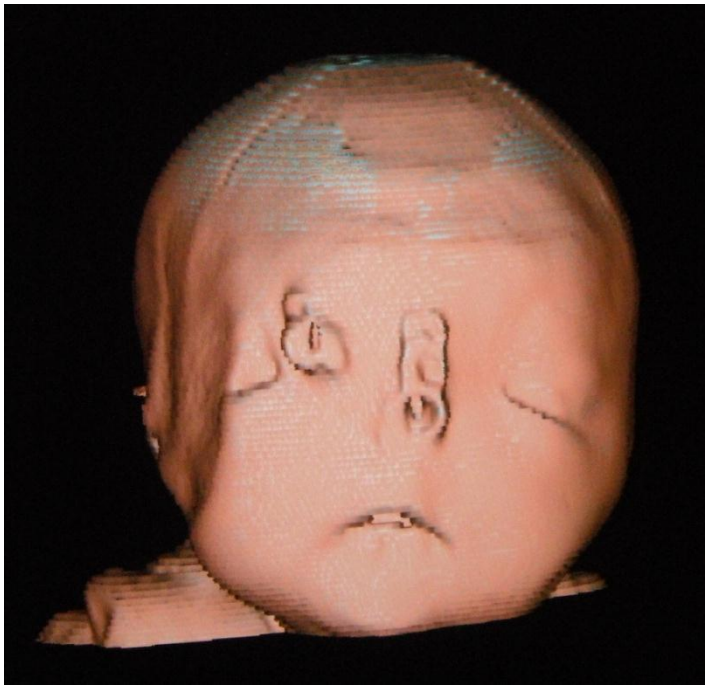


B

Figures-2.



A **B**



C

Figure-3.

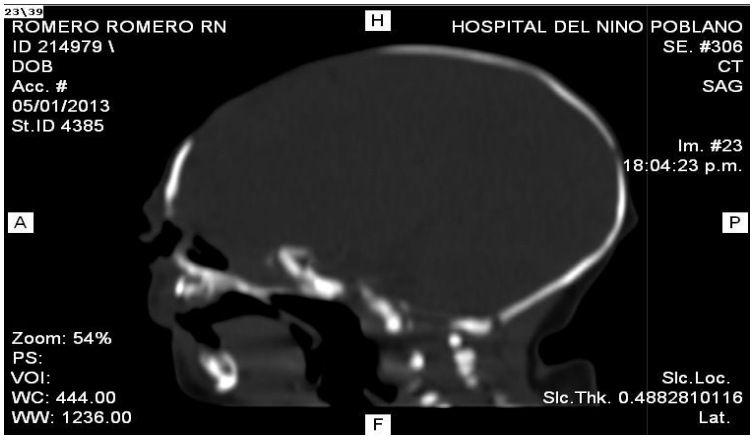


Figure-4.

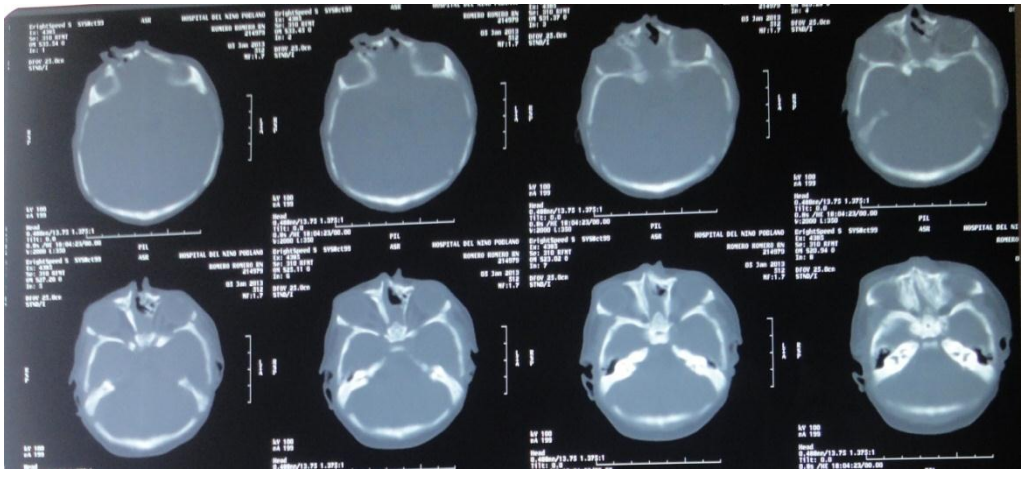


Figure-5.

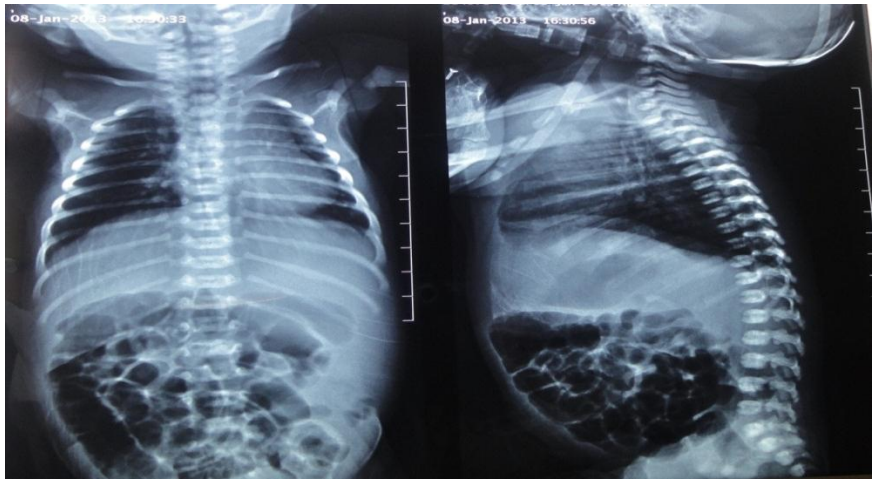


Figure-6.

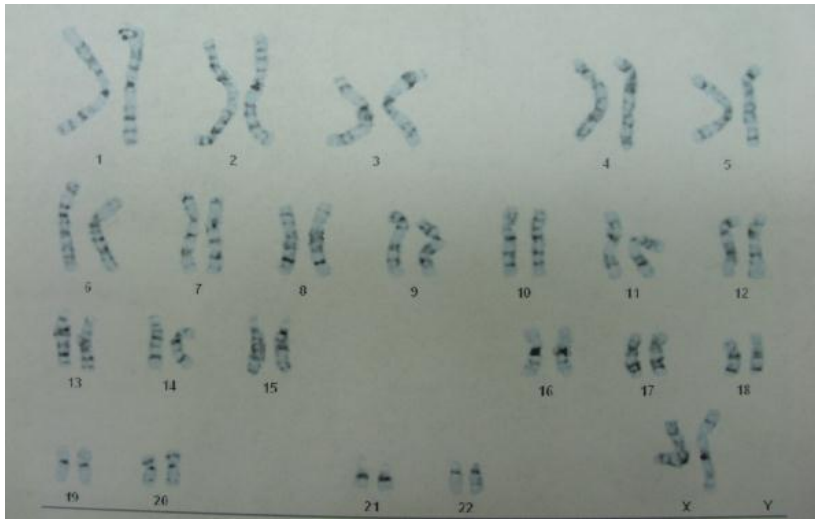


Figure-7.

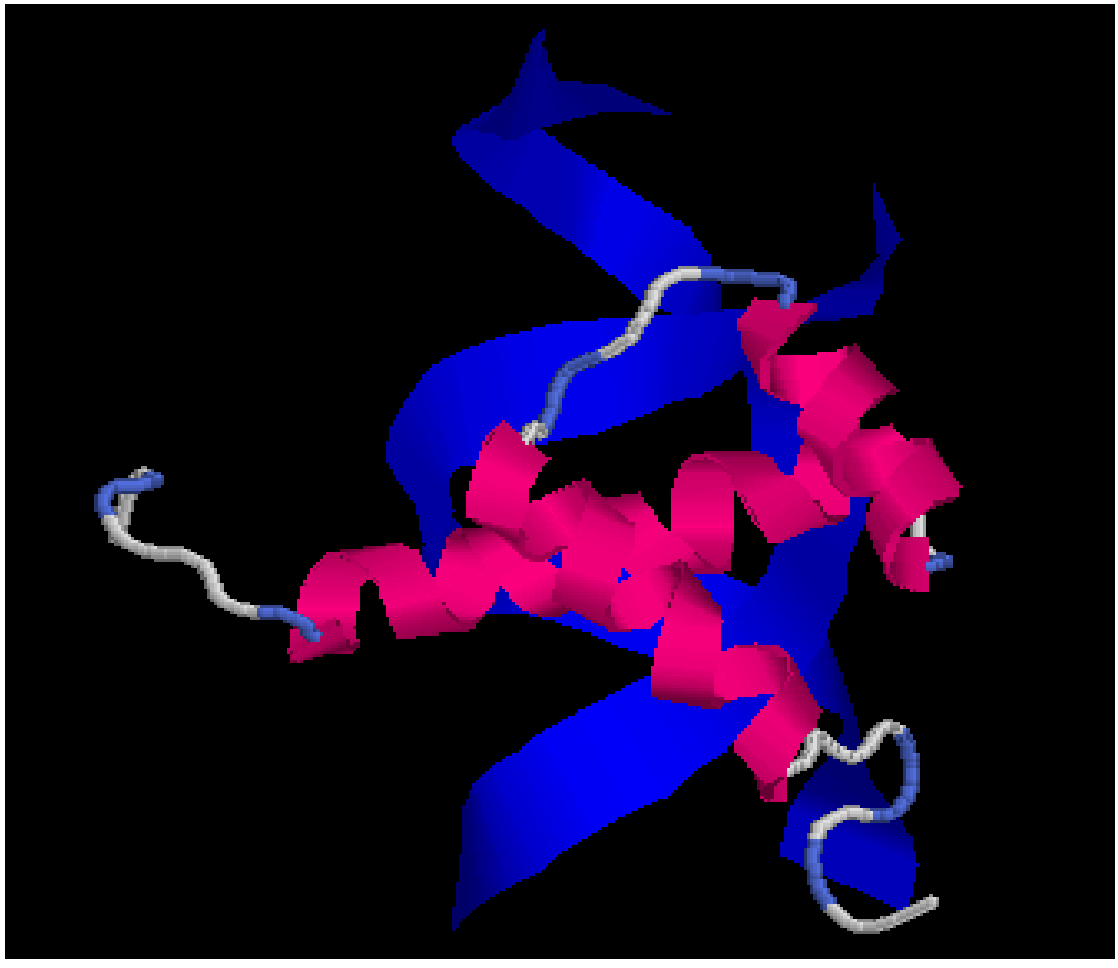


Figure-8.

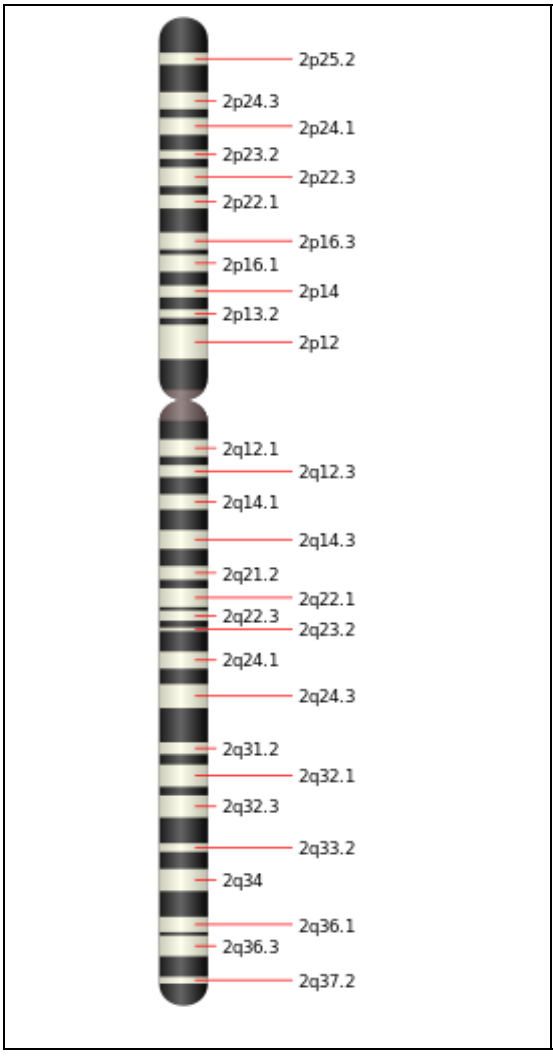


Figure-9.

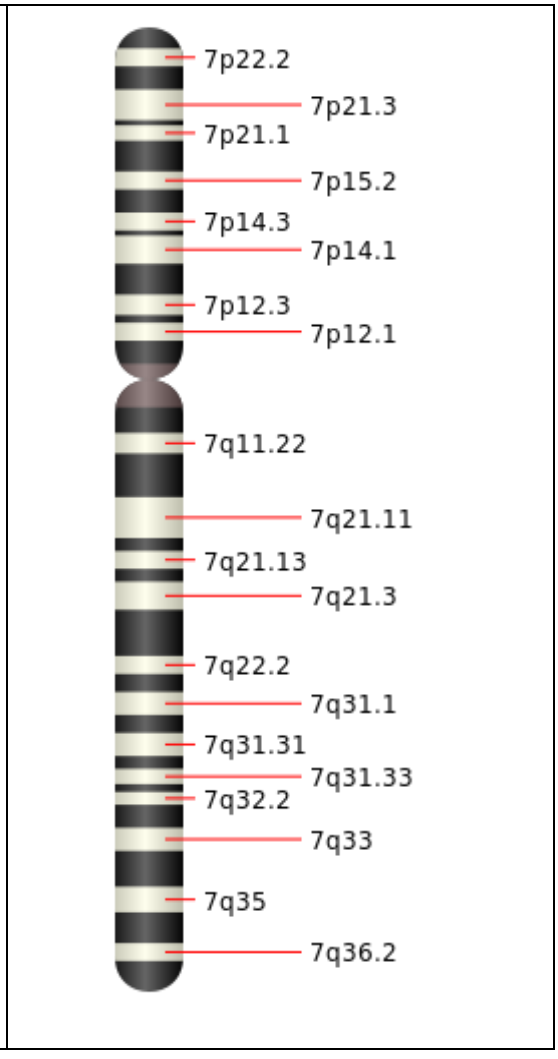


Figure-10.